REMARKS/ARGUMENTS

Status of Claims

Claims 1-7 were pending prior to this amendment.

Claims 1-7 have been rejected.

Claims 1 and 7 are cancelled.

Claim 8 is added. New claim 8 is directed to a compound recited in claim 2 in isolated form. Support for the subject matter of new claim 8 can be found in the specification as originally filed, for example, in Examples 1 through 5.

Claim 3 is amended to become an independent claim.

Claim 4 is amended to replace the word "formulation" with the word "composition." The amendment is supported by the specification as originally filed, specifically, from line 15 of page 14 through last line of page 15, with the specific word "composition" being used on line 15 of page 14. In addition, claim 4 is amended to change its dependency from claim 1 to claim 2

Claim 5 is amended to change its dependency from claim 1 to claim 2 and to include the phrase "which method comprises" at the end of the preamble.

No new matter has been added to the application by this amendment.

Rejection to Claims 1-4

Claims 1-4 stand rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Pande (U.S. Patent No. 6,359,005) in view of Wirth et al. (J. Pharm. Sci., 87(1), 31-39, 1998). Claim 1 as originally filed is directed to a pregabalin lactose conjugate or a pharmaceutically acceptable salts, ester, amide, and prodrug thereof. While Applicants believe claim 1 is patenable over the references cited, in order to expedite the allowance of other claims pending in this application, Applicant has cancelled claim 1, which renders the rejection moot.

Claims 2 and 3 are each directed to a limited number of specific compounds. Applicant respectfully submits that a prima facie case of obviousness has not been established with respect to claims 2 and 3, for reasons detailed below.

Applicants respectfully submit that there is no structural similarity between the compounds of claims 2 and 3, on the one hand, and pregabalin, on the other hand. Pande relates to the compound pregabalin. Pregabalin is a small, branched chain γ-amino acid, consisting of a 6-carbon alkyl chain, a primary amine, and a carboxylic acid function group. It has no rings in its structure and has a molecular weight of only 191 daltons. In comparison, the claimed compounds are much more complex in structures, each of which has two to three ring structures constituting the major portion of their overall structure. None of the compounds has a primary amine or a carboxylic acid functional group as pregabalin does. The nominal molecular weight of the compounds ranges from 303 to 465 daltons, which is significantly larger than that of pregabalin. The structure of the claimed compounds is not simply different from that of pregabalin; there is no structural similarity at all between the claimed compounds and pregabalin. Indeed, in making the rejection, the Examiner has not alleged structural similarity between the claimed compounds and the prior subject matter. The lack of structural similarity is in no way cured by the secondary reference, i.e. Wirth et al., which relates to fluoxetine hydrochloride, a compound bearing no structural similarity with any compounds of the invention. "For a chemical compound, a prima facie case of obviousness requires 'structural similarity between claimed and prior art subject matter . . . where the prior art gives reasons or motivation to make the claimed compositions'." Yamanouchi Pharmaceutical Co. ltd. V. Danbury Pharmacal. Inc., 231 F. 3d 1339, 1343; 56 USPQ2d 1641, 1644 (Fed. Cir. 2000), quoting in re Dillon, 919 F.2d 688, 692, 16 USPQ2d 1897, 1901 (Fed. Cir. 1990)(en banc) (emphasis added). Because the requirement of "structural similarity" has not been met in this case, a prima facie case of obviousness cannot be established.

Applicants also submit that there is no motivation to modify pregabalin, or to combine the references, to produce the claimed compounds. The Examiner alleges that "the motivation for doing so is provided by Pande, which suggests the use of pregabalin in the treatment of anxiety or epilepsy because of the nontoxic nature of the compound, ease of preparation and the ease of administration of the drug (see col. 3, lines 55-60)." Applicants believe, however, rather than motivating a person skilled in the art to modify the structure of pregabalin beyond recognition to arrive at the claimed invention, Pande

actually teaches way from doing so. Modification of pregabalin to such an extent would be against scientific wisdom. It is known in the art that properties of a compound, including biological, chemical, and physical properties, are closely related to the compound's molecular composition and structure and that significant changes in structure are expected to significantly change a compound's property, including its biological activities. Thus, in view of the striking structural differences between the claimed compounds and pregabalin, a person skilled in the art would not expect the claimed compounds to have a biological activity that is the same as, or similar to, that of pregabalin. Absent such expectation, there would be no motivation for a person skilled in the art to modify pregabalin to arrive at the claimed invention.

Further, there is no motivation to combine the teaching of Pande with Wirth et al. Regarding the teaching of Wirth et al, the Examiner states, "Wirth et al. teach the excellent composition and stability characteristics of lactose and its ability to undergo Maillard reactions to produce formulation, ..." (emphasis added) Applicants understand that by "its ability to undergo Maillard reactions to produce formulation" the Examiner alleges that Wirth et al. teach that Maillard reaction of lactose with the active agent is a desirable property in producing pharmaceutical formulations. Applicants respectfully submit that Wirth et al. teach the contrary, namely, Maillard reaction of lactose is undesirable and, therefore, should be avoided when selecting formulation ingredients. Wirth et al. disclose Maillard reaction of the active drug fluoxetine with lactose, an excipient in fluoxetine formulations. According to Wirth et al., this drug-excipient reaction causes "degradation," or "decomposition," of the formulation and formation of impurities in the formulated drug products, leading to reduced stability of the drug products. Specifically, the Examiner's attention is drawn to lines 3-5 of the Abstract, where the authors state, "We show that such formulation are inherently less stable than formulation with starch as the diluent due to the Mallard reaction between the drug, a secondary amine hydrochloride, and lactose." Further, in the passage immediately below Figure 7 on page 37, in describing the results of stress stability study with a fluoxetine capsule and a fluoxetine tablet, the authors state, "Both products displayed Maillard browning and produced 2, 3, and many other impurities. The results from the tablet (Figure 7) are comparable with decomposition profiles of the simple mixture of lactose,

drug and magnesium starate. However, the capsule was significantly less stable, showing formation of nearly 4% of 2 after 122 h at 85°C and a total impurity level of 13%." Because Mailard reaction leads to degradation or decomposition of the formulation, it is clear that Wirth et al does not suggest the desirability of the Maillard reaction of lactose with pregabalin. As the Court of Appeals for the Federal Circuit has held, the mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. (In re Mills, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990); MPEP 2143.01.) Because Wirth et al. do not suggest a desirability of Maillard reaction of lactose with the active agent, the teachings of the references cannot be properly combined.

Applicants further submit that there is no reasonable expectation of success in combining the teachings of both references to obtain the compounds of the invention. The Examiner asserts that one skilled in the art would have reasonable expectation of success in combining the teachings of both references to obtain the compounds of the invention and its pharmaceutical composition. The alleged basis for this assertion is that "Pande teaches pregabalin, its derivatives, and pharmaceutically acceptable salts in the treatment of anxiety or epilepsy (nervous system disorder), and Wirth et al. teach the excellent compression stability characteristics of lactose and its ability to undergo Maillard reactions to produce formulation." Applicants believe that such teaching does not carry with it a reasonable expectation of success. As is known in the art and is disclosed in Wirth et al., Maillard reaction is a multi-step complex chemical reaction, which involves multitude of intermediates and multitude of possible pathways and products. (Please see Wirth et al. first paragraph on page 1). As Wirth et al. also disclose, the identity of the end products of Maillard reaction is readily affected by reaction conditions, such as temperature, humidity, presence of other materials, etc. As Wirth et al. further disclose, products of Amadori rearrangement, which follows Maillard reaction, "are often unstable and are difficult to prepare, isolate, and characterize." (see Wirth et al. bottom of page 38). Given the complexity of the Maillard reaction, and the possibility and uncertainty of its end products, a person of skilled in the art would not have a reasonable expectation that the specific compounds of the invention would be produced by Maillard reaction of lactose with pregabalin.

Moreover, Wirth et al. have no disclosure as to any therapeutic utility for any Maillard reaction products of lactose with fluoxetine, let alone any suggestion that any specific products would have the same utility as the starting material fluoxetine. Rather, as Wirth et al. characterize the Maillard reaction products as "degradation products," "impurities," or "decomposition" products, it suggests that such products would not have the same utility as fluoxetine. Thus, in view of Wirth et al., a person of skilled in the art would not have reasonable expectation that pregabalin would undergo Maillard reaction with lactose to produce the specific claimed compounds that would have a biological activity that is the same as or similar to that of pregabalin.

Claim 4, as amended, is directed to a pharmaceutical composition comprising at least one compound recited in claim 2. Because claim 2 is not obvious for reasons as explained above, claim 4, which includes the limitation of claim 2, is not obvious either.

Rejection to Claim 5-7

Claims 5-7 stand rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Pande (U.S. Patent No. 6,359,005) in view of Wirth et al. (J. Pharm. Sci., 87(1), 31-39, 1998). Claim 7 is cancelled, which renders the rejection moot. Claim 5, as amended, and claim 6 are directed a method of treatment using a compound recited in claim 2. Because Applicants believe that the compounds recited in claim 2 are non-obvious as explained above, claims 5 and 6, which both include limitations of claim 2, are also non-obvious.

New claim 8 is dependent from claim 2. As with claims 5 and 6, because Applicants believe that claim 2 is non-obvious as explained above, claim 8, which includes the limitations of claim 2, is non-obvious as well.

In view of the above remarks and amendments, Applicants respectfully request reconsideration of the application, withdrawal of the rejections to the claims, and timely issuance of Notice of Allowance in this case.

Respectfully submitted,

Date: 8/3/04

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